Amendments to the Specification

Please replace the paragraph beginning at page 1, line 15, with the following rewritten paragraph:

Methods utilizing mass spectrometry for the analysis of a target polypeptide have been taught wherein the polypeptide is first solubilized in an appropriate solution or reagent system. The type of solution or reagent system, e.g., comprising an organic or inorganic solvent, will depend on the properties of the polypeptide and the type of mass spectrometry performed and are well-known in the art (see, e.g. Vorm et al. (1994) Anal. Chem. 66:3281 (for MALDI) and Valaskovic et al. (1995) Anal. Chem. 67:3802 (for ESI)). Mass spectrometry of peptides is further disclosed, e.g. in WO 93/24834 by Chait et al.

Please replace the paragraph beginning at page 5, line 1, with the following rewritten paragraph:

~~PCT/EP/04396~~ PCT/EP97/04396 (WO 98/07036) teaches a process for determining the status of an organism by peptide measurement. The reference teaches the measurement of peptides in a sample of the organism which contains both high and low molecular weight peptides and acts as an indicator of the organism's status. The reference concentrates on the measurement of low molecular weight

peptides , i.e. below 30,000 Daltons, whose distribution serves as a representative cross-section of defined controls. Contrary to the methodology of the instant invention, the '396 patent strives to determine the status of a healthy organism, i.e. a "normal" and then use this as a reference to differentiate disease states. The present inventors do not attempt to develop a reference "normal", but rather strive to specify particular markers whose presence, absence or relative strength/concentration in disease vs. normal is diagnostic of at least one specific disease state or whose up-regulation or down-regulation is predictive of at least one specific disease state, whereby the presence of said marker serves as a positive indicator useful in distinguishing disease state. This leads to a simple method of analysis which can easily be performed by an untrained individual, since there is a positive correlation of data. On the contrary, the '396 patent requires a complicated analysis by a highly trained individual to determine disease state versus the perception of non-disease or normal physiology.

Please replace the paragraph beginning at page 37, line 3, with the following rewritten paragraph:

Figure 1 is a photograph of a tricine gel DEAE 1 (Elution) comparing [[a]] normal ~~specimen~~ versus Type II Diabetes;

Figure 2 is a trypsin digested spectra graph depicting the characteristic profile of the ion 1211 (SEQ ID NO:1);

Figure 3 is a trypsin digested spectra graph depicting the characteristic profile of the ion 2173 (SEQ ID NO:2);

Figure 4 is a photograph of a tricine gel HiQ3 (scrub)comparing [[a]] normal ~~specimen~~ versus Type II Diabetes; and

Figure 5 is a trypsin digested spectra graph depicting the characteristic profile of the ion 1190 (SEQ ID NO:3).

Please replace the paragraph beginning at page 40, line 16, with the following rewritten paragraph:

Preparatory Protocols:

Any of these protocols may be selected from a column flow-through stream, a column elution stream, or a column scrub stream.

Hi Q is a strong anion exchanger made of methyl acrylate co-polymer with the functional group: $-N^{+}(CH_3)_2$;

Hi S is a strong cation exchanger made of methyl acrylate co-polymer with the functional group: $-SO_3^{-}$;

DEAE is a diethylaminoethyl which is a weak cation exchanger made of methyl acrylate co-polymer with the functional group:

$-N^{+}(C_2H_5)_2$;

PS is phenyl ~~sepharose~~ SEPHAROSE;

BS is buytl ~~sepharose~~ SEPHAROSE.

Please replace the paragraph beginning at page 41, line 6, with the following rewritten paragraph:

Note that the supports, i.e. methyl acrylate and ~~sepharose~~ SEPHAROSE are different, but non-limiting examples, as the same functional group on different supports will function, albeit possibly with different effects.

Please replace the paragraph beginning at page 41, line 10, with the following rewritten paragraph:

DEAE Column Protocol:

1) Cast 200 µl of 50% slurry;
2) Equilibrate column in 5 bed volumes of 50 mM tricine pH 8.8 (binding buffer);
3) Dissolve 25 µl of sera in 475 µl of binding buffer;
4) Wash column in 5 bed volumes of binding buffer;
5) Elute column in 120 µl of 0.4 M Phosphate buffer (PB) pH 6.1;
6) Elute column in 120 µl of 50 mM citrate buffer pH 4.2;
7) Scrub column with 120 µl sequentially with each of 0.1% ~~triton~~ TRITON , 1.0% ~~triton~~ TRITON and 2% SDS in 62.5 mM [[Tris]] TRIS pH 6.8.

Please replace the paragraph beginning at page 42, line 1, with the following rewritten paragraph:

Butyl ~~sepharose~~ SEPHAROSE column protocol:

1) Cast 150 µl bed volume column;
2) Equilibrate column in 5 bed volumes of 1.7 M $(NH_4)_2SO_4$ in 50 mM PB pH 7.0 (binding buffer);
3) Dissolve 35 µl of sera in 465 µl of binding buffer and apply;
4) Wash column in 5 bed volumes of binding buffer;
5) Elute column in 120 µl of 0.4 M $(NH_4)_2SO_4$ in 50 mM PB pH 7.0;
6) Elute column in 120 µl of 50 mM PB pH 7.0;
7) Scrub column with 120 µl sequentially with each of 0.1% ~~triton~~ TRITON ,1.0% ~~triton~~ TRITON and 2% SDS in 62.5 mM [[Tris]] TRIS pH 6.8.

Please replace the paragraph beginning at page 42, line 16, with the following rewritten paragraph:

Phenyl ~~sepharose~~ SEPHAROSE column protocol:

1) Cast 150 µl bed volume column;
2) Equilibrate column in 5 bed volumes of 1.7 M $(NH_4)_2SO_4$ in 50 mM PB pH 7.0 (binding buffer);

3) Dissolve 35 µl of sera in 465 µl of binding buffer and apply;

4) Wash column in 5 bed volumes of binding buffer;

5) Elute column in 120 µl of 0.2 M $(NH_4)_2SO_4$ in 50 mM PB pH 7.0;

6) Elute column in 120 µl of 50 mM PB pH 7.0;

7) Scrub column with 120 µl sequentially with each of 0.1% ~~triton~~ TRITON , 1.0% ~~triton~~ TRITON and 2% SDS in 62.5 mM [[Tris]] TRIS pH 6.8.

Please replace the paragraph beginning at page 43, line 7, with the following rewritten paragraph:

HiQ Anion Exchange Mini Column Protocol:

1) Dilute sera in sample/running buffer;

2) Add HiQ resin to column and remove any air bubbles;

3) Add ultrafiltered (UF) water to aid in column packing;

4) Add sample/running buffer to equilibrate column;

5) Add diluted sera;

6) Collect all the flow-through fraction in ~~Eppendorf~~ EPPENDORF tubes until level is at resin;

7) Add sample/running buffer to wash column;

8) Add elution buffer and collect elution in ~~Eppendorf~~ EPPENDORF tubes.

Please replace the paragraph beginning at page 43, line 20, with the following rewritten paragraph:

HiS Cation Exchange Mini Column Protocol:

1) Dilute sera in sample/running buffer;
2) Add HiS resin to column and remove any air bubbles;
3) Add UF water to aid in column packing;
4) Add sample/running buffer to equilibrate column for sample loading;
5) Add diluted sera to column;
6) Collect all flow through fractions in ~~Eppendorf~~ EPPENDORF tubes until level is at resin;
7) Add sample/running buffer to wash column;
8) Add elution buffer and collect elution in ~~Eppendorf~~ EPPENDORF tubes.

Please replace the paragraph beginning at page 44, line 9, with the following rewritten paragraph:

Illustrative of the various buffering compositions useful in this technique are:

Sample/Running buffers: including but not limited to Bicine buffers of various molarities, pH's, NaCl content, ~~Bis-Tris~~ BIS-TRIS buffers of various molarities, pH's, NaCl content, Diethanolamine

of various molarities, pH's, NaCl content, Diethylamine of various molarities, pH's, NaCl content, Imidazole of various molarities, pH's, NaCl content, Tricine of various molarities, pH's, NaCl content, Triethanolamine of various molarities, pH's, NaCl content, [[Tris]] TRIS of various molarities, pH's, NaCl content.
Elution Buffer: Acetic acid of various molarities, pH's, NaCl content, Citric acid of various molarities, pH's, NaCl content, HEPES of various molarities, pH's, NaCl content, MES of various molarities, pH's, NaCl content, MOPS of various molarities, pH's, NaCl content, PIPES of various molarities, pH's, NaCl content, Lactic acid of various molarities, pH's, NaCl content, Phosphate of various molarities, pH's, NaCl content, Tricine of various molarities, pH's, NaCl content.

Please replace the paragraph(first amended on February 13, 2002) beginning at page 46, line 8, with the following rewritten paragraph:

As a result of these procedures, the disease specific markers complement C3f precursor ion having a molecular weight of about 1211.67 daltons and a sequence of SEQ ID NO:1, complement C3 precursor having a molecular weight of about 2172.99 daltons and a sequence of SEQ ID NO:2, complement C3 precursor having a molecular weight of about 1190.6210 daltons and a sequence of SEQ

ID NO:3, apolipoprotein E ion having a molecular weight of about 1333 shown in Band 5 and complement C3 precursor having a molecular weight of about 1497 also shown in Band 5 of Figure 4, predictive of Type II diabetes were found.

Please replace the paragraph beginning at page 49, line 10, with the following rewritten paragraph:

The specific disease markers which are analyzed according to the method of the invention are released into the circulation and may be present in the blood or in any blood product, for example plasma, serum, cytolyzed blood, e.g. by treatment with hypotonic buffer or detergents and dilutions and preparations thereof, and other body fluids, e.g. [[CSF]] cerebrospinal fluid (CSF), saliva, urine, lymph, and the like. The presence of each marker is determined using antibodies specific for each of the markers and detecting specific binding of each antibody to its respective marker. Any suitable direct or indirect assay method may be used to determine the level of each of the specific markers measured according to the invention. The assays may be competitive assays, sandwich assays, and the label may be selected from the group of well-known labels such as radioimmunoassay, fluorescent or chemiluminescence immunoassay, or immunoPCR technology. Extensive discussion of the known immunoassay techniques is not required here

since these are known to those of ~~skilled~~ skill in the art. See Takahashi et al. (Clin Chem 1999; 45(8): 1307) for a detailed example of an assay.

Please replace the paragraph beginning at page 67, line 2, with the following re-written paragraph:

The instant invention involves the use of a combination of preparatory steps in conjunction with mass spectroscopy and time-of-flight detection procedures to maximize the diversity of biopolymers which are verifiable within a particular sample. The cohort of biopolymers verified within such a sample is then viewed with reference to their ability to evidence at least one particular disease state; thereby enabling a diagnostician to gain the ability to characterize either the presence or absence of [[said]] at least one disease state relative to recognition of the presence and/or the absence of [[said]] the biopolymer, predict disease risk assessment, and develop therapeutic avenues against [[said]] the disease.